

**REMARKS**

Claims 1-141 were pending in the application. Claims 15-40, 50-62, 64-73, 75, 84-86, and 94-141, directed to non-elected inventions, have been canceled without prejudice to further prosecution in a divisional application(s). Claims 1, 2, 5, 11, and 14 have been canceled in view of the amendments made herewith. New claims 142-174 have been added. Claims 12-14, 88, 89, 91, and 92 have been amended to correct for dependencies and formalities. Thus, upon entry of this Amendment, claims 9-14, 41-49, 88-89, 91-92, and 142-174 are pending in the application.

Support for the amendment to claim 9 can be found throughout the specification, including at least at page 134, lines 10-14. Support for the amendment to claims 10 and 11 can be found throughout the specification, including at least at Table 2 (Appendix A) and in the claims as originally filed. Support for the amendment to claim 15 can be found throughout the specification, including at least at page 9, lines 35-37 and at page 17, lines 33-34.

Support for new claims 144, 145, 156, and 157 can be found throughout the specification, including at least at Table 2 (Appendix A). Support for new claims 146-148 and 161-163 can be found at least at page 126, lines 6-11 and at Table 2 (Appendix A). Support for new claim 151 can be found in the specification, including at least at page 58, lines 35-36, at page 134, lines 10-14, and at Table 11. Support for new claim 143 and 152 can be found throughout the specification, including at least at page 33, lines 16-24. Support for new claims 153-155, 158-160, and 164-166 can be found throughout the specification, including at least at Table 2 (Appendix A) and in the claims as originally filed. Support for new claims 167-170 can be found in the specification, including at least at page 44, lines 23-27. Support for new claims 172-174 can be found in the claims as originally filed and in the specification at page 44, lines 18-19 and at pages 91-95.

No new matter has been added. Applicants request that the amendments to the specification and claims be entered. The foregoing claim amendments and cancellation should in no way be construed as an acquiescence to any of the Examiner's rejections and

were made solely to expedite prosecution of the present application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

#### Supplemental Information Disclosure

Applicants submit herewith a Supplemental Information Disclosure Statement (IDS) which contains references which Applicants are aware of as being related to the claimed subject matter. Applicants point out that none of the references cited in the Supplemental IDS teaches or describes the claimed invention, *i.e.*, a fully human, high affinity anti-IL-12 antibody.

#### Indication of Allowability of Claims 41-49

Applicants gratefully acknowledge the Examiner's indication that claims 41-49 are allowable.

#### Interview Summary

Applicants acknowledge and thank the Examiner for the interview with Applicants' attorney on August 19, 2003, in which claims were discussed, as well as references which are submitted herewith in the Supplemental IDS.

#### Rejection of Claims 2-14, 63, 74, 76-83, 87-93 Under 35 U.S.C. § 112, First Paragraph

##### *I. Rejection of Claims 2-14, 63, 74, 76-83, 87-93 Under 35 U.S.C. § 112, First Paragraph*

The Examiner has rejected claims 2-14, 63, 74, 76-83, 87-93 under 35 U.S.C. 112, first paragraph, stating that the specification "does not enable any person skilled in the art to which it pertains...to make or use the invention commensurate with the scope of the claims." Applicants respectfully traverse this rejection. In the interest of expediting

prosecution of the present application, claims 2-8, 63, 74, 76-83, 87, and 93 have been cancelled, rendering the foregoing rejection moot in view of these claims.

Amended claim 9 and new claims 151 and 153 are directed to a **fully human antibody** which binds human IL-12 with high affinity. As amended, claim 9 is directed to an isolated human antibody, or antigen-binding portion thereof, that binds to human IL-12 and dissociates from human IL-12 with a  $K_d$  of  $1 \times 10^{-10}$  M or less and a  $k_{off}$  rate constant of  $1 \times 10^{-3} \text{ s}^{-1}$  or less, as determined by surface plasmon resonance. New claim 151 is directed to an isolated human antibody, or an antigen-binding portion thereof, which dissociates from human IL-12 with a  $K_d$  of  $1 \times 10^{-10}$  M or less and binds to an epitope on the p40 subunit of human IL-12. In one embodiment, the fully human antibody which binds human IL-12 is a neutralizing antibody which inhibits phytohemagglutinin blast proliferation in an *in vitro* PHA assay with an  $IC_{50}$  of  $1 \times 10^{-7}$  M or less. In another embodiment of the claimed invention, the fully human antibody which binds human IL-12 is a neutralizing antibody which inhibits human IFN $\gamma$  production with an  $IC_{50}$  of  $1 \times 10^{-10}$  M or less. New claim 153 describes a neutralizing isolated human antibody, or antigen-binding portion thereof, that binds to human IL-12 and dissociates from human IL-12 with a  $k_{off}$  rate constant of  $1 \times 10^{-3} \text{ s}^{-1}$  or less, as determined by surface plasmon resonance.

The Examiner rejects claims, including, for example, claim 9, which recite functional limitations, because the said claims lack "clear and definite structural limitations." Applicants traverse this rejection based on the premise that Applicants should not be limited to antibodies defined by sequences, as suggested by the Examiner, because the instant specification describes **fully human antibodies which bind IL-12 with high affinity**. Applicants provide numerous examples of fully human antibodies which meet the limitations of claim 9, *i.e.*, bind IL-12 with high affinity. Thus,

Applicants submit that the claims should not be limited to an antibody with a specific sequence.

The specification teaches multiple examples of high affinity antibodies, as well as the process of modifying anti-IL-12 antibodies with these characteristics to further improve them. Thus, Applicants teach the process of obtaining anti-IL-12 human antibodies with high affinity, as well human anti-IL-12 antibodies with neutralizing capability. For example, as described at page 44, lines 18-27 and in Example 1 of the specification, Applicants describe the cloning and characterization of anti-IL-12 antibody Joe 9, which was obtained by screening a human VL and VH cDNA library by phage display with human IL-12 (hIL-12). In order to obtain antibodies with improved binding properties, the CDR3 region of Joe 9 was mutated. Applicants teach that CDR3 variants of Joe 9 were created using site-directed PCR mutagenesis (see page 136, line 21 to page 137, line 4 of the specification). The variant heavy and light chains were then studied in various "mix and match" combinations for improved binding affinity and neutralization characteristics (see page 44, line 27 to page 45, line 25; page 138, line 29 to page 139, line 12; and Table 2 of the specification). As shown in Table 2, Applicants teach multiple combinations of variant heavy and light chains, including clone 101-11, which was chosen for further modification based on its notable binding and neutralization characteristics. Applicants teach that clone 101-11 was mutagenized to further improve the binding and neutralization characteristics (see Example 1D, page 139 of PCT publication). Following random mutagenesis of clone 101-11, Applicants identified clone 103-14 which has improved characteristics over clone 101-11. Clone 103-14 was then selected for random mutagenesis, wherein Applicants describe the identification of antibody Y61 (see page 139, line 25 to page 141, line 10 of specification).

Antibody Y61 has improved affinity characteristics over clone 103-14 and was, therefore, selected for site-directed mutation at specific hypermutation and contact

positions to still further improve the antibody's characteristics (see page 53, lines 15-25; page 141, line 14 to page 143, line 6 of PCT specification). The mutational analysis of Y61 led to the identification of antibody J695, which has improved characteristics, e.g., neutralization, over antibody Y61. Thus, Applicants teach a lineage of antibodies from Joe 9 to J695, wherein each generation has improved characteristics, e.g., binding and/or neutralization, compared to the previous generation. The antibody lineage of the invention is described in Figure 1, including the amino acid sequences for each antibody.

Based on the detailed description of the sequence information and functional analysis of the antibody lineage, Applicants should not be limited to one particular antibody sequence but rather to an antibody with common features as clearly described in the specification. Furthermore, one of ordinary skill in the art could take an antibody described early in the lineage, *e.g.*, clone 103-14, and perform mutagenesis as described in the instant specification and arrive at an antibody with similar binding features as those described by Applicants but with a different amino acid sequence, (see page 54, lines 23-30 and page 58, line 10 to page 60, line 6 of the specification).

The Examiner rejects claims 90-93 for lack of support from the specification, stating that the claims recite a "multitude of disparate therapeutic agents" but fail to support these agents in a pharmaceutical composition comprising the claimed antibody "beyond the mere mention of therapeutic agents." Claims 90 and 93 have been canceled, thus rendering the rejection moot in view of these claims. Claims 91 and 92 describe therapeutic agents in a pharmaceutical composition in combination with the claimed antibody. In the specification, Applicants teach use of these additional agents for treatment of IL-12 associated disorders, including, for example, inflammatory disorders such as inflammatory bowel disease (see page 92, lines 24-25 and page 93, line 24). Applicants teach in the specification that the list of additional therapeutic agents recited in claims 91 and 92 are agents commonly used to treat diseases associated with IL-12,

and, therefore, one of ordinary skill in the art would recognize that said therapeutic agents would be useful in treating a disease or condition which is treated with the claimed antibody (see page 91, line 32 to page 92, line 10 of the specification). Thus, Applicants submit that the instant specification adequately describes and enables the claimed invention.

*II. Rejection of Claims 2-14, 63, 74, 77-83, 87-93 Under 35 U.S.C. § 112, First Paragraph*

The Examiner has rejected claims 2-14, 63, 74, 77-83, 87-93 under 35 U.S.C. 112, first paragraph, stating that the specification does not "does not reasonably convey to one skilled...that the inventor(s), at the time the application was filed, had possession of the claimed invention." Applicants respectfully traverse this rejection. In the interest of expediting prosecution of the present application, claims 2-8, 63, 74, 77-83, 87, and 93 have been cancelled, rendering the foregoing rejection moot.

The Examiner states that the specification "only describes the structure of J695 antibody...and does not describe the structure of any other antibody that binds to IL-12 or mutant thereof." In contrast to the Examiner's assertion, Applicants provide numerous examples of high affinity human antibodies which bind IL-12, as described in detail above. For these reasons, Applicants submit that one of ordinary skill in the art could follow the teachings of the specification and arrive at a fully human antibody with the same functional limitations taught by Applicants, *i.e.*, binds IL-12 with high affinity, but with different structural characteristics, *e.g.*, amino acid sequences. It is Applicants' position that the ordinarily skilled artisan can reproduce an antibody having the claimed binding characteristics, including the precise antigen-binding characteristics of, for example, the J695 antibody, in view of the instant disclosure.

Accordingly, applicants request that this objection to the specification and rejection of claims 2-14, 63, 74, 76-83, and 87-93 under 35 U.S.C §112, first paragraph, be reconsidered and withdrawn.

Rejection of Claims 2-14, 63, 74, 76-83, and 87 Under 35 U.S.C. § 112, Second Paragraph

*I. Rejection of Claims 2-14, 74, 76-83 and 87 Under 35 U.S.C. § 112, Second Paragraph*

The Examiner has rejected claims 2-14, 74, 76-83 and 87 under 35 U.S.C 112, second paragraph, stating that the claims are vague and indefinite for recitation of the mutations at selective positions and for use of the phrase "such that". Applicants respectfully traverse this rejection. In the interest of expediting prosecution of the present application, claims 2-8, 74, 76-83, and 87 have been cancelled, thus rendering the foregoing rejection moot. Applicants submit that amended claims 9-14 do not include mention of mutations or the phrase "such that." Thus, Applicants respectfully request that the rejection of claims 9-14 be removed.

*II. Rejection of Claim 63 Under 35 U.S.C. § 112, Second Paragraph*

The Examiner has rejected claim 63 under 35 U.S.C 112, second paragraph, for use of the phrase "one or more amino acid substitutions." Applicants respectfully traverse this rejection. In the interest of expediting prosecution of the present application, claim 63 has been cancelled, thus rendering the foregoing rejection moot.

*III. Rejection of Claim 87 Under 35 U.S.C. § 112, Second Paragraph*

The Examiner has rejected claim 87 under 35 U.S.C 112, second paragraph, for

being unclear and indefinite. Applicants respectfully traverse this rejection. In the interest of expediting prosecution of the present application, claim 87 has been cancelled, thus rendering the foregoing rejection moot.

Rejection of Claim 1 Under 35 U.S.C. § 102

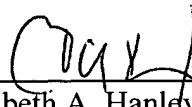
The Examiner has rejected claim 1 under 35 U.S.C 102, for lacking novelty in view of Trinchieri (US Patent No. 5,811,523). Applicants respectfully traverse this rejection. In the interest of expediting prosecution of the present application, however, claim 1 has been cancelled, thus rendering the foregoing rejection moot.

SUMMARY

Cancellation of and/or amendments to the claims should in no way be construed as an acquiescence to any of the Examiner's objections and/or rejections. The cancellation of the claims is being made solely to expedite prosecution of the above-identified application. Applicants reserve the option to further prosecute the same or similar claims in the present or another patent application. In view of the foregoing remarks, reconsideration of the rejections and allowance of all pending claims is respectfully requested. The amendments made to the claims are not related to any issues of patentability.

If a telephone conversation with Applicants' Attorney would expedite the prosecution of the above-identified application, the examiner is urged to call Applicants' Attorney at (617) 227-7400.

Respectfully submitted,



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